

Clinical & Refractive Optometry is pleased to present this continuing education (CE) article by Dr. John Jantzi entitled **Effect of High-Dose Antioxidant and Zinc Supplementation on Progression of Age-Related Macular Degeneration**. In order to obtain a 1-hour Council of Optometric Practitioner Education (COPE) approved CE credit, please refer to page 118 for complete instructions.

Effect of High-Dose Antioxidant and Zinc Supplementation on Progression of Age-Related Macular Degeneration

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ABSTRACT

Age-related macular degeneration (AMD), a disorder of the retinal pigment epithelium, is the leading cause of blindness for people aged 65 and older. Due to an aging population, the number of AMD cases is expected to triple in the next 25 to 40 years. There is, as yet no cure for this disease. The Age-Related Eye Disease Study (AREDS) was the first large clinical trial to investigate the effect of high-dose ocular supplementation on progression of AMD. Among patients with advanced AMD in one eye or with intermediate AMD, high levels of both antioxidants and zinc reduced the risk of progression to advanced AMD and risk of at least 15 letters of vision loss from baseline in 5 years by 25% and 19%, respectively. AREDS evaluated progression of AMD in 3640 patients, aged 55 to 80, with early to advanced AMD. Participants were randomized to daily tablets containing: 1) antioxidants (15 mg of beta carotene, 500 mg of vitamin C, and 400 IU of vitamin E); 2) zinc (80 mg zinc oxide and 2 mg cupric oxide); 3) antioxidants plus zinc; or 4) placebo. This article presents an overview of AMD focusing on the role of vitamin supplementation and discusses AREDS and its implications for clinical practice.

BACKGROUND

AMD is the leading cause of visual impairment and blindness for people over 65 in the United States and elsewhere.¹ The United Nations estimates that between 20 and 25 million people are affected worldwide, a number that is expected to triple over the next 30 to 40 years, as the population ages.² Each year, almost 78,000 Canadians are diagnosed with this disease, and this is expected to triple within the next 25 years.³ Currently, more than 50% of

the Canadian National Institute of the Blind's clients have macular degeneration.³

Much remains unknown about the AMD's pathophysiology and ways to slow its progression. Laser photocoagulation and photodynamic therapy benefit some patients with advanced AMD. AREDS was undertaken to assess the impact of high doses of ocular supplementation on progression of AMD and reduction in vision loss. The results of this first large randomized clinical trial to study ocular supplementation were published in the October 2001 issue of *Archives of Ophthalmology*.¹ However, there still appears to be some confusion about how to apply the study's recommendations to clinical practice and choose ocular supplements for particular AMD patients.

AGE-RELATED MACULAR DEGENERATION

“Dry” versus “Wet” Macular Degeneration

The exact etiology of AMD is unknown. This disease is a degenerative disorder of the retinal pigment epithelium (RPE) that causes loss of central vision, leaving only peripheral vision intact. The macula is the portion of the central retina with the greatest concentration of photoreceptors and provide high resolution visual acuity. With advancing age, the cells of the RPE become less efficient. Early stages of AMD are characterized clinically by the development of drusen, which are amorphous, acellular debris in the basement membrane of the RPE that are seen as yellow spots within the macula. While small drusen are commonly present in the macula as a consequence of aging, the presence of soft drusen, pigment abnormalities, and well-defined areas of RPE loss (geographic atrophy) is commonly termed “dry” AMD.⁴ Dry AMD progresses slowly over many years. The time to legal blindness varies between 5 and 10 years.²

The development of choroidal neovascularization, pigment epithelial detachment, and an exudative process is commonly termed “wet” AMD.⁴ Wet AMD evolves rapidly. AREDS reported a 47% risk of developing advanced AMD in 6 years in an eye with intermediate AMD, or in an eye where the fellow eye had advanced AMD.¹ The wet form of AMD comprises approximately 15% of AMD cases,⁴ but it is more sight threatening and accounts for 90% of severe visual loss in elderly people.²

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Fig. 1 Fundus photograph of a study eye with Category 2 (dry) AMD shows extensive intermediate drusen. (Reprinted with permission from: *Atlas of Ophthalmology, Philadelphia: Current Medicine, 2000: 335*)

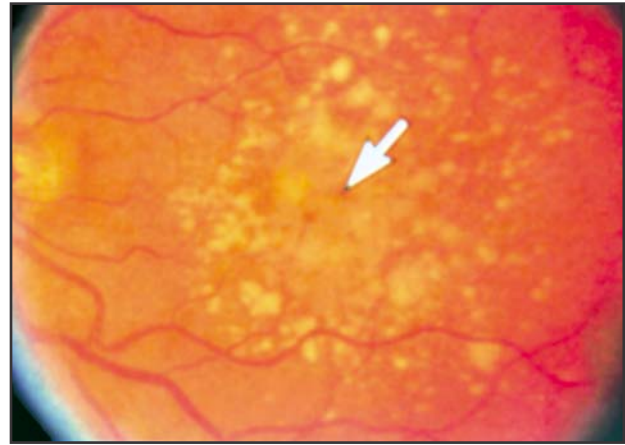


Fig. 2 Fundus photograph of a study eye with Category 3 (dry) AMD showing drusenoid pigment epithelial detachment (arrow). (Reprinted with permission from: *Atlas of Ophthalmology, Philadelphia: Current Medicine, 2000: 335*)

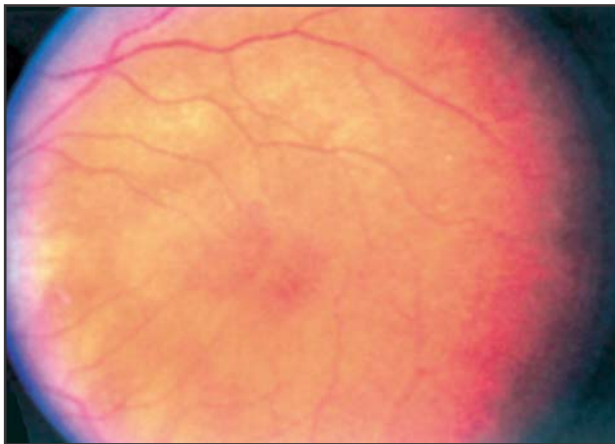


Fig. 3 Fundus photograph of a nonstudy eye with Category 4 (wet) AMD showing classic choroidal neovascularization. (Reprinted with permission from: *Atlas of Ophthalmology, Philadelphia: Current Medicine, 2000: 337*)

Risk Factors and Clinical Features

In addition to older age, identifiable AMD risk factors include female sex, white race, blue eyes, cigarette smoking, and low dietary intake of carotenoids. Genetic factors have been increasingly shown to play a role. Cardiovascular disease and increased exposure to sunlight have been inconsistently identified as risk factors.⁴

The most common symptoms of AMD are blurred central vision, metamorphopsia, and reduced vision. Patients report that images become blurry, colors are hard to distinguish, and central vision is blocked by dark or empty spaces. When shown a piece of graph paper, they might say that the squares look distorted and the lines look wavy. Ophthalmic examination of the fundus reveals patchy choroidal atrophy in dry AMD and macular edema in wet AMD, often associated with retinal hemorrhages and lipid exudate around the macula.²

Role of Ocular Vitamins and Minerals

Much remains unknown about the development of the disease. It has been proposed that antioxidants may prevent cellular damage in the retina by reacting with free radicals produced in the process of light absorption.⁵ In the outer retina, polyunsaturated fatty acids may be adversely affected by free radical production and oxidation. Antioxidants may play a role in maintaining the integrity of choroidal blood vessels that supply the macular region of the retina.

In 1994, Seddon et al⁶ investigated the role of dietary intake of carotenoids and vitamins A, C, and E on the development of AMD. Based on food frequency questionnaire results from 356 patients with advanced AMD and 520 control subjects, they suggest that high consumption of dark green, leafy vegetables might decrease the risk of developing advanced AMD.

Two other trials assessed supplementation for patients with AMD.¹ A small, randomized trial suggested a benefit of large doses of zinc on visual acuity in persons with AMD. Researchers from another randomized trial report that 4 years of supplementation with 500 IU of vitamin E had little benefit in reducing the development or progression of AMD in a population of 1193 volunteers.

AGE-RELATED EYE DISEASE STUDY (AREDS)

Study Rationale

Because of the controversy surrounding the protective effect of antioxidants and zinc, and to better understand the natural history and risk factors for AMD and cataract, the National Eye Institute of the National Institutes of Health initiated a 10-year cohort study: AREDS.⁷ The AMD

AMD Category	Number of Patients	Characteristics of Patients' Eyes	
		Study Eye [†]	Fellow Eye
1	1117	< 5 small drusen‡	same as study eye
2	1063	multiple small drusen, or at least 1 intermediate drusen, or pigment abnormalities	same as study eye or category 1
3	1621	extensive intermediate drusen, or at least 1 large druse, or noncentral geographic atrophy, with or without pigment abnormalities	same as study eye, or category 1 or 2, or VA < 20/32 not due to AMD
4	956	no advanced AMD§	advanced AMD or VA < 20/32 due to AMD

* Category 1 AMD patients were included in the cataract trial but excluded from the AMD trial
[†] All patients had VA > 20/32, no advanced AMD, and no disqualifying lesions in the study eye
[‡] Drusen size: small = <63 µm, intermediate = 63-124 µm, and large = ≥125 µm
[§] Advanced AMD = central geographic atrophy or choroidal neovascularization

Patient Group	Progression to Advanced AMD		Visual Acuity Loss ≥15 Letters from Baseline	
	OR (95% CI)	Risk Reduction	OR (95% CI)	Risk Reduction
Antioxidants	0.76 (0.55-1.05)	17%	0.85 (0.63-1.14)	–
Zinc	0.71 (0.52-0.99)	21%	0.83 (0.62-1.11)	–
Antioxidants + zinc	0.66 (0.47-0.92)	25%	0.73 (0.54-0.99)	19%
Placebo	1.00	–	1.00	–

* Average follow-up was 6.3 years

component of AREDS evaluated the effect of taking about 5 to 15 times the recommended daily allowances (RDAs) of antioxidants (vitamin C, vitamin E, and beta carotene) and zinc on the development of advanced AMD.

From 1992 to 1998, AREDS enrolled subjects from 11 retinal specialty clinics who were aged 55 to 80 and who had a best-corrected visual acuity of 20/32 (6/10) or better with no advanced AMD in the study eye. Participants first undertook a 1-month run-in with placebo to demonstrate compliance. They had to agree to take two fairly large tablets 2 times daily for up to 8 years.

Three Disease Categories, Four Treatment Regimens

The AMD trial comprised 3640 participants who were grouped into three AMD categories as summarized in Table I. The 1063 patients with Category 2 AMD had multiple, small (<63 µm) drusen, or at least 1 intermediate (63-124 µm) druse, or pigment abnormality in the study eye. The 1621 patients with Category 3 AMD had extensive intermediate drusen, or at least 1 large (≥125 µm) druse, or noncentral geographic atrophy, with or without pigment abnormality, in the study eye. The 956 patients with Category 4 AMD had advanced AMD or VA <20/32 (<6/10) due to AMD in the nonstudy eye. Figures 1 to 3 illustrate representative eyes in these three categories.

Study subjects were randomized to one of four supplement regimens with the following daily content:

1) antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg), 2) zinc (zinc oxide, 80 mg; cupric oxide, 2 mg), 3) antioxidants plus zinc, or 4) placebo. Copper was added to zinc formulations to prevent copper deficiency associated with high levels of zinc. AREDS supplements were given as two tablets in the morning and two tablets at night.

Since vitamins degrade slightly during their shelf lives, tablets used in this trial were manufactured to have the following minimum contents: 7160 IU of vitamin A (beta carotene), 113 mg of vitamin C (ascorbic acid), 100 IU of vitamin E (dl-alpha tocopheryl acetate), 17.4 mg of zinc (zinc oxide), and 0.4 mg of copper (cupric oxide).

Study subjects were followed for an average of 6.3 years. Stereoscopic fundus photographs of the macula were taken at baseline and annually starting 2 years after randomization. Ophthalmic examinations, including visual acuity determinations, were done every 6 months. At 5 years, it was estimated that 71% of participants took 75% or more of their study tablets. Biochemical assays revealed that serum levels antioxidants and zinc were increased over baseline levels among subjects taking these supplements.

Study Outcomes

The two primary study outcomes were: 1) color fundus photographic documentation of progression to advanced AMD and 2) at least a 15-letter decrease in visual acuity

score from baseline. The latter loss of vision is equivalent to a doubling or more of the initial visual angle, eg 20/20 (6/6) to 20/40 (6/12) or worse, or 20/50 (6/15) to 20/200 (6/60) or worse.

Category 2 patients only had a 1.3% probability of progression to advanced AMD over 5 years. However, the reduction in risk of progressing to advanced AMD for Category 3 and 4 patients who received antioxidants, zinc, or combination were 17%, 21%, and 25%, respectively. The only statistically significant reduction in rates of at least a 15-letter visual acuity loss occurred in patients assigned to receive antioxidants plus zinc. The reduction in risk of this visual acuity loss was 19%, as shown in Table II.

There were few side effects. Participants in the antioxidant arms more frequently reported yellow skin (8.3% vs 6.0%, $p=0.008$). Genitourinary hospitalizations (eg, urinary tract infections, prostatic hyperplasia, stress incontinence) were more frequent in patients randomized to the zinc arms (7.5% vs 4.9%, $p=0.001$).

Interpreting AREDS Results

Several factors must be taken into consideration when interpreting AREDS findings. First, the study participants were relatively well nourished compared to the general population. Second, the retinal outcomes were based on fundus photography rather than fluorescein angiography, which might delay the identification of advanced AMD events. Third, odds ratio reductions are greater than estimates of relative risk reductions. Finally, it is not known for how long someone at risk for progression to advanced AMD should use supplements.

Two carotenoids, lutein and zeaxanthin, were considered for inclusion in the formulation during the AREDS planning phase, because they are concentrated in the macula. However, at AREDS initiation, neither carotenoid was readily available. Beta carotenoid was readily available and was being used in a trial for heart disease and cancer. After AREDS was underway, it was determined that smokers who take 15 mg/day of beta carotenoid are at increased risk of lung cancer. Whether lutein or zeaxanthin can be substituted for beta carotene and, if so, the optimal dose(s) remains to be determined. The AREDS dose of vitamin C (500 mg/day) is about 5 times the dietary intake in the general population. The study's doses of vitamin E (400 IU/day) and zinc oxide are about 13 times and 5 times the RDA, respectively. These levels can only be obtained by supplementation.

In Canada, three companies market high-dose antioxidant and zinc supplements that are promoted specifically for eye health. The supplements are ICaps (Alcon Canada Inc., Mississauga, ON), Ocuvite Capsules, Ocuvite Plus, and newly launched Ocuvite PreserVision

(Bausch & Lomb, Markham, ON), and Vitalux AREDS (Novartis Pharmaceuticals Canada, Inc., Mississauga, ON). All of these supplements contain different amounts of ingredients. Only Ocuvite PreserVision, at a dosage of two tablets twice daily is equivalent to the AREDS formulation.

Chang et al⁸ recently reported on the use of dietary supplements by 108 AMD patients seen in an Edmonton retinal specialty clinic. Although 85 patients (79%) were taking dietary supplements and 73 patients (68%) were taking at least 1 AREDS ingredient, the mean dosages of beta carotene, vitamin C, vitamin E, and zinc were all well below those recommended in the AREDS. This underdosing may be due to the absence until now of a supplement in Canada that exactly matches the AREDS formulation.

CONCLUSION

The AREDS group recommends, "Persons older than 55 years should have dilated eye examinations to determine their risk of developing advanced AMD. Those with extensive intermediate size drusen, at least 1 large druse, noncentral geographic atrophy in 1 or both eyes, or advanced AMD, or vision loss due to AMD in 1 eye, and without contraindications such as smoking, should consider taking a supplement of antioxidants plus zinc such as used in this study."¹ Chang et al⁸ add that despite high awareness and high prevalence of ocular dietary supplementation among AMD patients, these individuals may not be receiving the doses recommended in AREDS. □

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